Towards a decision-aid tool in the case of chemotherapy treatment for low-grade glioma

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Interdisciplinary project:

CRAN
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Yann Gaudeau
Meriem Ben Abdallah (PhD 12/2016)
new PhD from 10/17 ?

IECL - Inria-team BIGS
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C.H.R.U. Nancy
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Marie Blonski (hospital practitioner, PhD)

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Medical context: Diffuse Low-Grade Glioma

asymptomatic ↪
few symptoms ↪
functional prognosis ↪
bad vital prognosis ↪

Grade(ANOCEF)	
Low-Grade	I II
High-Grade	III IV

↩ slow growth: 4 mm/year ED

↩ quick growth : $>$ 8 mm/year

- Cerebral tumor
- median age : 35 years, survival median : 15 years, *(Duffau & al 04, Cancer)*
- 750 new cases by year in France *(Blonski 11, thèse de médecine)*
- diffuse aspect *(ANOCEF 12)*
- slow evolution with 4 mm/year spontaneous linear growth of equivalent diameter *(Mandonnet 03, Ann Neurol)*
- no treatment $\Rightarrow$ anaplasic transformation (evolution to high-grade) *(Bracard, Taillandier & al 06, Jour Radio)*

Therapeutic strategy

surgery
and/or chemotherapy TMZ, PCV
and/or radiotherapy

$\Downarrow$

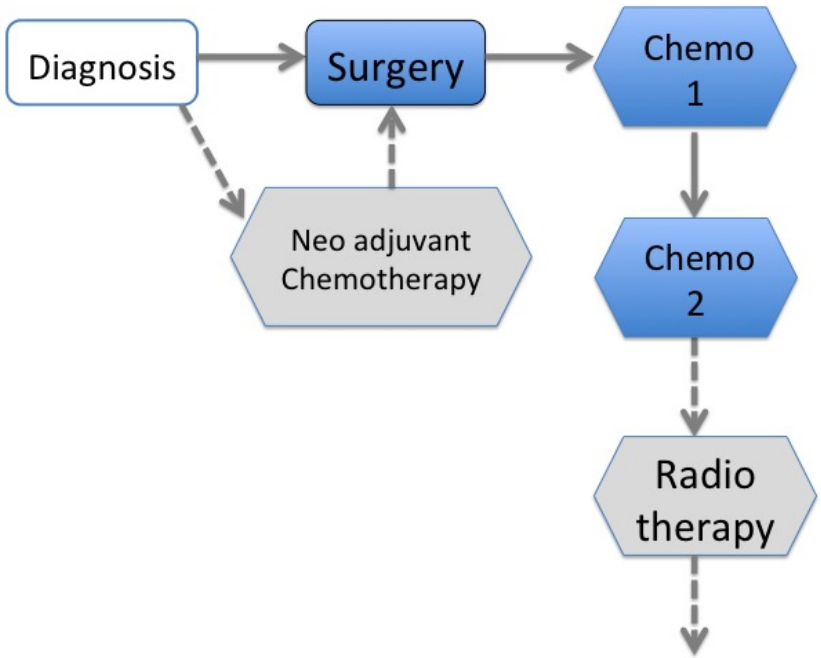
Aim: control of the tumor evolution in order to extend patient's lifetime
tumor diameter = good predictor of the evolution of DLGGs
(Mandonnet 08 Neurosurgical rw)

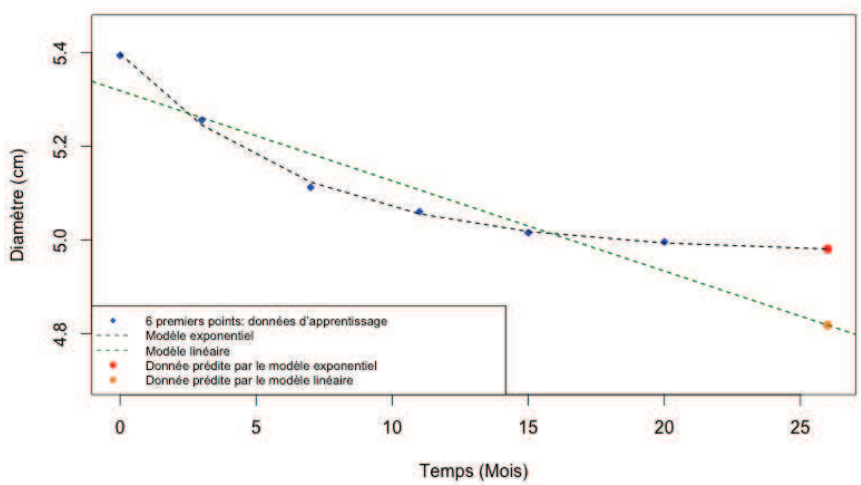
$\Downarrow$

longitudinal supervision of tumor's diameter evolution

$\Downarrow$

volume estimation from MRI datasets: security ?



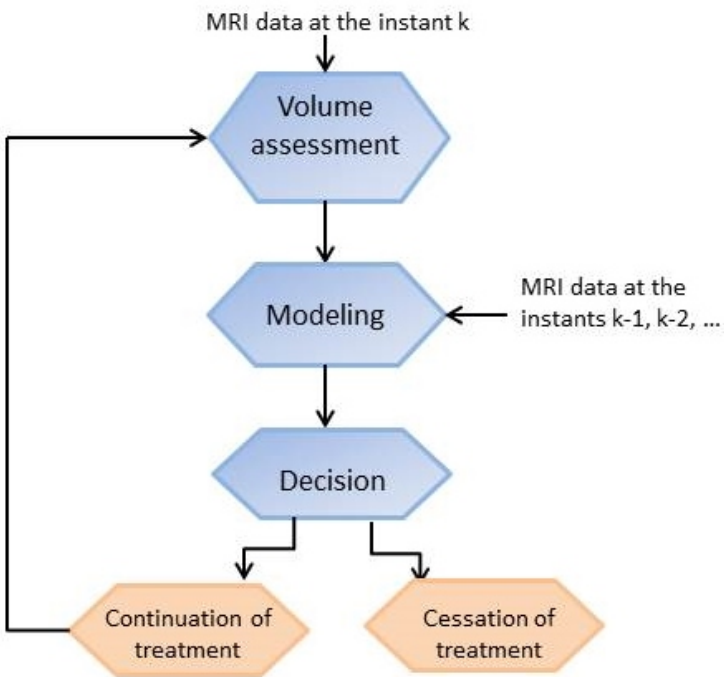


Our aim

Crucial questions posed by the oncologists to be answered:

- identifying subgroups of patients for chemotherapy
- determining the best time to initiate or stop chemotherapy
- evaluating the optimal time to perform surgery, or otherwise radiotherapy

personnalised treatment $\Rightarrow$ tool for the current medical practice



proposed procedure to determine the best time to stop chemotherapy

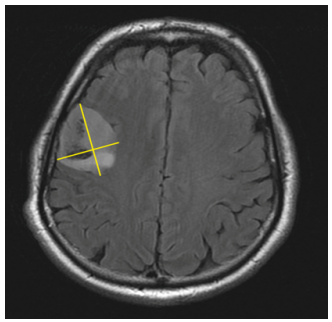
First phase: tumor volume estimation

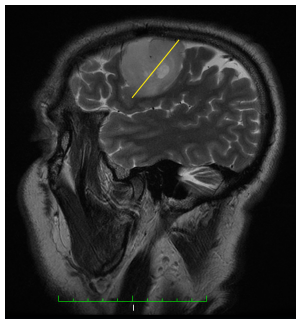
still in progress
Reliability of the methods used to estimate the volume :

- 3-diameter method
- software-based reconstruction from manual segmentation
- semi-automatic method

Questions: reliability and reproducibility
Impact on the segmentation of the individual practitioner, and of the factors: years of experience, medical speciality ?
with respect to the others methods ?

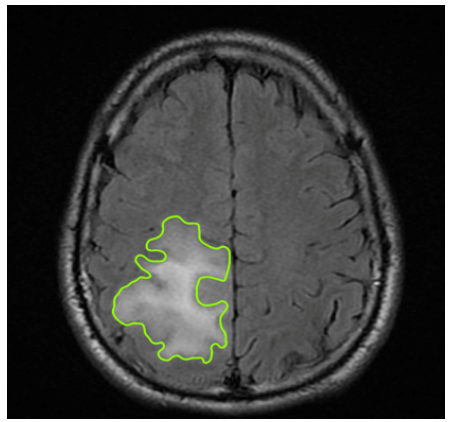
3-diameter Method





- 2 largest diameters in axial plane and the largest one in sagittal or coronal plane
- ellipsoidal approximation of the tumor volume:
  $V \simeq \frac{D_1 \times D_2 \times D_3}{2}$

Software-based reconstruction from manual segmentation

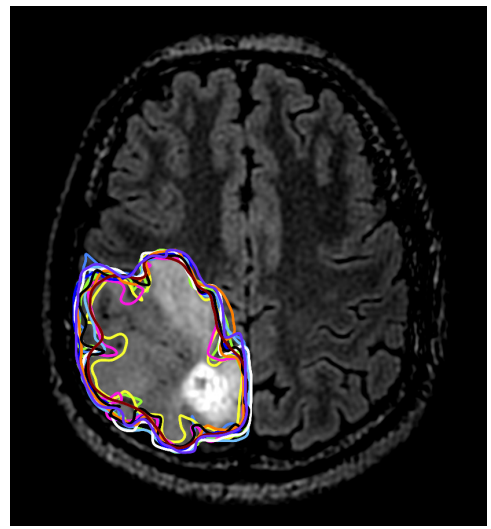


- digitized MRI, calculus of tumor volume from manual segmentations by Osirix software

Subjective test of reproducibility

Materials:

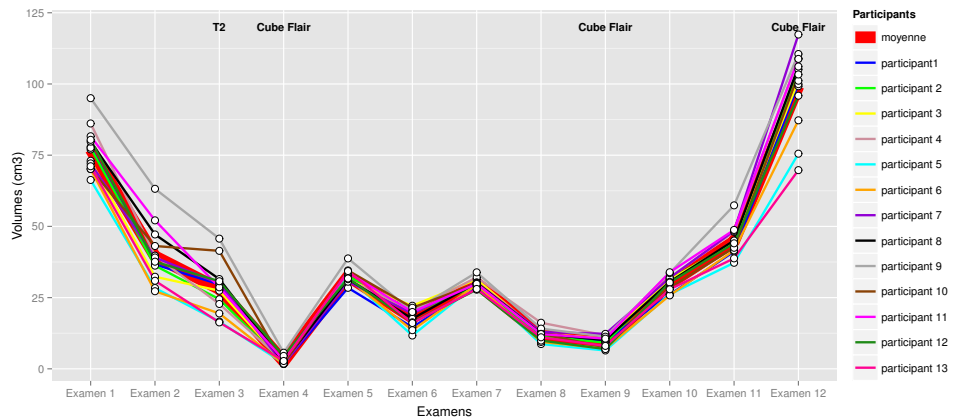
- one expert neuroradiologist selected 12 longitudinal MRI in the axial plane from 9 patients: 11 FLAIR-weighted (3 Cube-FLAIR), 1 T2-weighted.
- Osirix software
- Living Lab PROMETEE, TELECOM Nancy (standardized environment, ITU-BT.500-13 recommendations)
- panel of 13 participants
- test procedure: visual test, training dataset, delineation of the 12 exams (5 mn. break in half-time)



Results:

- variability between participants: one-way analysis of variance $\Rightarrow$ **no significant impact on the tumor volume variable**
- variability by specialty and years of experience: Fisher's exact test on the standard deviation of the standard volume $\Rightarrow$ **no significant impact on the tumor volume variable**
- Objective metrics: **Values of COV, AI, pixellic IV confirm the statistical results**

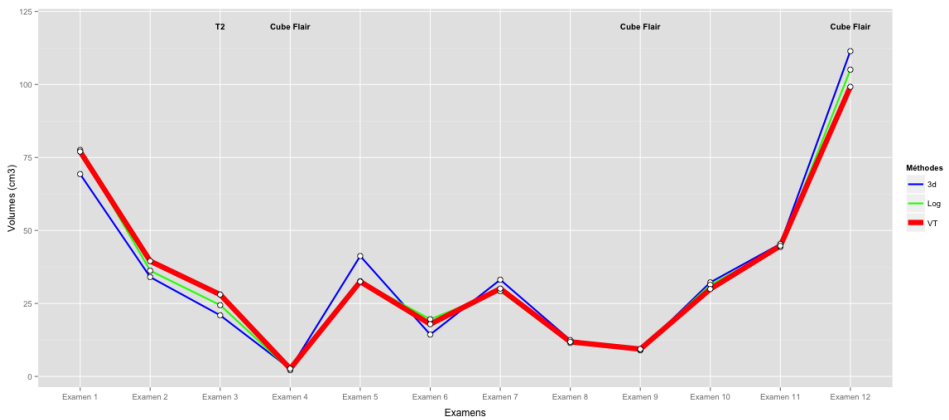
$$COV_j = \frac{\sigma_j}{\overline{x}_j}; AI_{(i,i'),j} = 1 - \frac{2 \mid x_{i,j} - x_{i',j} \mid}{x_{i,j} + x_{i',j}}; IV = 1 - \frac{A_{M_i} \cap A_{M'_i}}{A_{M_i} \cup A_{M'_i}}$$



Comparaison with the 3-diameter method

Materials:

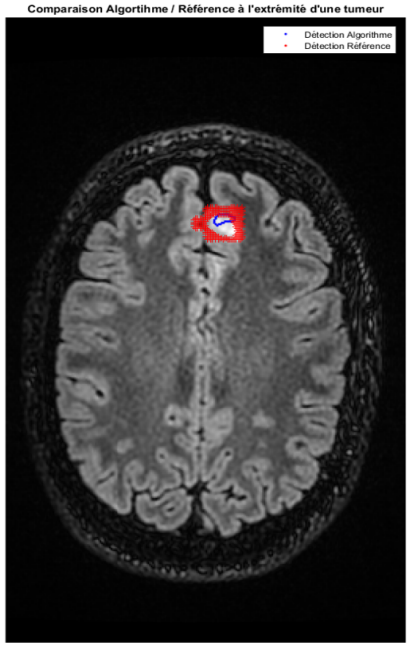
- preceeding 12 exams in the axial plane + sagittal(11) or coronal(1) plane associated
- 1 participant from the test, close to the average of all the segmented tumor volumes (ground truth)
- Wilcoxon signed-rank test on all tumor volumes : with a significance level of 5 %, **we do not reject the equality hypothesis** between 3-diameter and manual segmentation methods

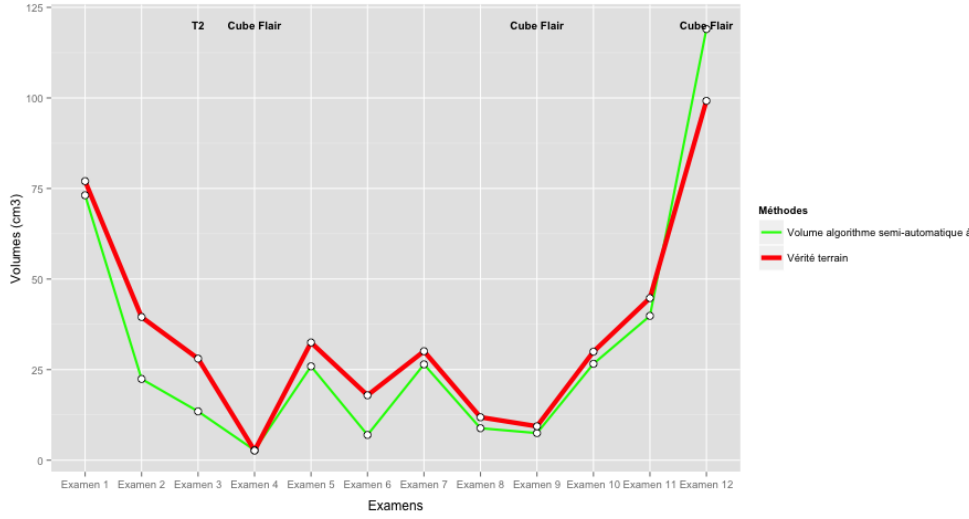


	Advantages	Disadvantages
3D	quick, easy for pre-surgery tumor	overestimate the volume, difficult in post-treatment
Osirix	reproducible accurate, easy	time-consuming

First works on semi-automatic segmentation

- Partnership with LIO Laboratory (C.H.R.U. Montréal, Pr J. De Guise, post-doc MBA)
- semi-automatic segmentation algorithm from Zhou & al *(EMBC 16)*
- Procedure: initialization by manual segmentation on 6 MRI in order to generate a 3D mesh, splitting of the mesh in axial slices then 2D delineation in each interest slide, Level-set algorithm applied on the 2D delineations
- MRI from test, ground truth = mean of the segmented volumes
- Computation time: 15-185 s





Results:

- Wilcoxon signed-rank test **rejects equality hypothesis** of the two methods
- tendency to under-segmentation
- good result for Cube-Flair 4 and 9
- segmentation algorithm applied to knees, considered improvements on this application domain

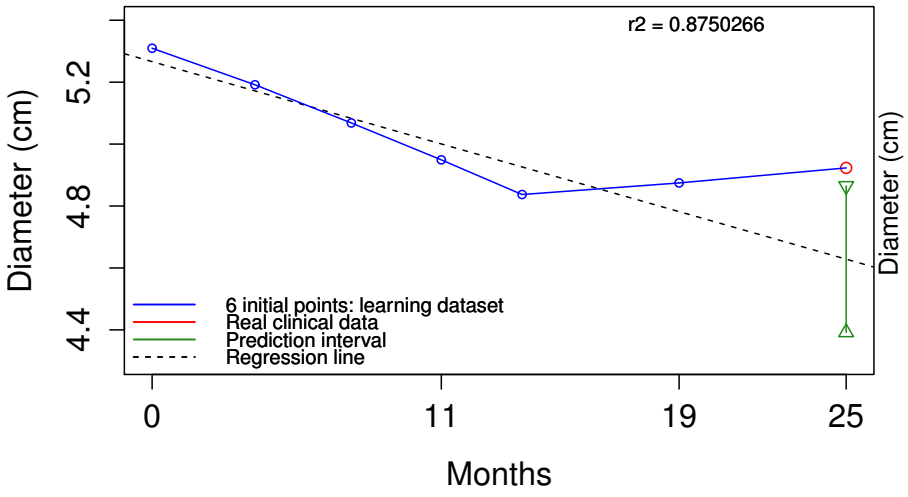
	Advantages	Disadvantages	Recommendations
3D	quick, easy for pre-surgery tumor	overestimate the volume, difficult in post-treatment	no digitised MRI, pre-surgery
Osirix	reproducible accurate, easy	time-consuming	all MRI except Cube-Flair
S-AUTO S	quick, good results on Cube-Flair	post-treatment under-segmentation	Cube-Flair

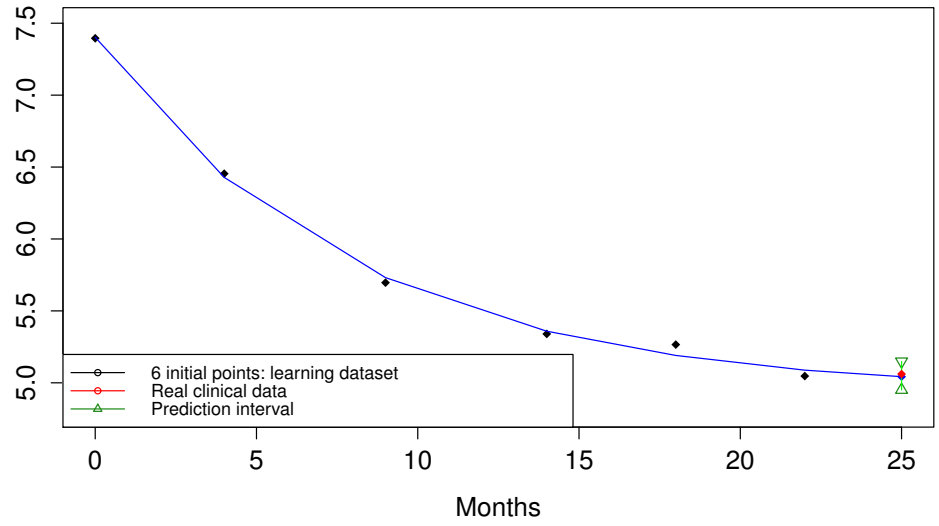
- comparison between methods to estimate the tumor volume
- medical recommendations to assure a more secure follow-up of the tumor evolution
- Trials with ITK SNAP: method strongly dependant on initialisation parameters (based on a priori good knowledge of the tumor: localization, shape)

Second phase: modelling of DLGG under chemotherapy

- tumor diameter: good predictor of the evolution of DLGGs *(Mandonnet 03, Ann Neurol)*
- state-of-the-art models: microscopic *(Ribba & al 2012, Rojas & al 2016)* or macroscopic *(Swanson& al 2000, Mandonnet & al 2003)* approach
- Our approach: data-driven, very simple to implement
- Database of 55 patients from both Nancy and Montpellier, France University Hospitals (CHRU)
- inclusion criteria: established histologic diagnosis of DLGG, first-line TMZ chemotherapy, assessment of the tumor volume with Osirix and manual segmentation method
- 2 models based on classical regression technics, with AICc criteria for model selection
- 38 following a linear model, 4 an exponential model, 13 no identifiable model (hieratic behaviour)

2 examples





linear model

$$D = b_O + b_1 T + \varepsilon$$

Warning message: alarming regrowth of the tumor, the patient is not reponding any more to treatment

exponential model

$$D = a_O - a_1 e^{-a_2 T} + \varepsilon$$

Message: expected decrease of the tumor, improved response to treatment

-

- encouraging but multifactorial problem
- IDH mutation, 1p19q codeletion are now considered as prognostic and/or predictive factors *(Louis & al 2016, 2016 OMS classification)*
- identifiable biological, anatomopathological factors ?
- in the database of 55: only 19 with known mutation and codeletion statuses

$\Downarrow$

Necessity of a bigger database

- more patients, more molecular's factors, more MRIs
- difficulty in data collection

Conclusion and Future work

- First two simple models that operates on 42 patients, encouraging, need to be enhanced
- Perspective 1: Bigger database

  30 variables selected by neuro-oncologists: 10 patient variables, 13 treatment variables, 7 tumor variables

  partnership with Montpellier, NENO base

  variable selection, unsupervised and/or supervised classification...
- Perspective 2: complete phase 1 with semi-automatic method (future, partnership with Montréal LIO) ; second subjective test to assess intra-participant variability
- Perspective 3: practical tool with additionnal image processing features

References

Meriem Ben Abdallah, Marie Blonski, Sophie Wantz-Mézières, Yann Gaudeau, Luc Taillandier et Jean-Marie Moureaux
Predictive models for diffuse low-grade glioma patients under chemotherapy
Statistical evaluation of manual segmentation of a diffuse low-grade glioma MRI dataset
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